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The influence of sentinel lymph node tumour burden on additional lymph node involvement and disease-free survival in cutaneous melanoma - a retrospective analysis of 392 cases

Guggenheim, M ; Dummer, R ; Jung, F J ; Mihic-Probst, D ; Steinert, H ; Rousson, V ; French, L E ; Giovanoli, P

Abstract: Twenty per cent of sentinel lymph node (SLN)-positive melanoma patients have positive non-SLN lymph nodes in completion lymph node dissection (CLND). We investigated SLN tumour load, non-sentinel positivity and disease-free survival (DFS) to assess whether certain patients could be spared CLND. Sentinel lymph node biopsy was performed on 392 patients between 1999 and 2005. Median observation period was 38.8 months. Sentinel lymph node tumour load did not predict non-SLN positivity: 30.8% of patients with SLN macrometastases ($>$ or $=2$ mm) and 16.4% with micrometastases ($<$ or $=2$ mm) had non-SLN positivity ($P=0.09$). Tumour recurrences after positive SLNs were more than twice as frequent for SLN macrometastases (51.3%) than for micrometastases (24.6%) ($P=0.005$). For patients with SLN micrometastases, the DFS analysis was worse ($P=0.003$) when comparing those with positive non-SLNs (60% recurrences) to those without (17.6% recurrences). This difference did not translate into significant differences in DFS: patients with SLN micrometastasis, either with ($P=0.022$) or without additional positive non-SLNs ($P<0.0001$), fared worse than patients with tumour-free SLNs. The 2-mm cutoff for SLN tumour load accurately predicts differences in DFS. Non-SLN positivity in CLND, however, cannot be predicted. Therefore, contrary to other studies, no recommendations concerning discontinuation of CLND based on SLN tumour load can be deduced.

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The Influence of Sentinel Lymph Node Tumor Burden on Additional Lymph Node Involvement and Disease-Free Survival in Cutaneous Melanoma – A retrospective Analysis of 392 Cases

Running Title: The influence of sentinel tumor burden in melanoma

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Abstract

Background: 20% of sentinel lymph node (SLN) positive melanoma patients have positive non-SLN lymph nodes in completion lymph node dissection (CLND). We investigated SLN tumor load, non-Sentinel-positivity and disease-free survival (DFS), to assess whether certain patients could be spared CLND.

Gelöscht: studied the correlation between

Patients and Methods: SLN-biopsy was performed on 392 patients between 1999 and 2005. Median observation period was 38.8 months.

Results: SLN tumor load did not predict non-SLN-positivity: 30.8% of patients with SLN macro_metastases (mets) ($\geq 2\text{mm}$) and 16.4% with micro mets ($\leq 2\text{mm}$) had non-SLN-positivity ($p=0.09$). Tumor recurrences after positive SLNs were more than twice as frequent for SLN macrometastases (51.3%) than for micrometastases (24.6%) ($p=0.005$). For patients with SLN micrometastases, the DFS-analysis was worse ($p=0.003$) when comparing those with positive non-SLNs (60% recurrences) to those without (17.6% recurrences). This difference did not translate into significant differences in DFS: Patients with SLN micrometastasis either with ($p=0.022$) or without additional positive non-SLNs ($P<0.0001$), fared worse than patients with tumor-free SLNs.

Kommentar [D1]: Immer mets

Gelöscht: metastases

Gelöscht: es

Gelöscht: correspond

Gelöscht: Both p

Conclusions: The 2mm-cut-off for SLN tumor load accurately predicts differences in DFS in contrast to non-SLN-positivity in CLND. Therefore, no recommendations concerning discontinuation of CLND based on SLN tumor load can be deduced.

Gelöscht: .

Gelöscht: N

Gelöscht: , however, cannot be predicted

Gelöscht: contrary to other studies,

Key Words: Melanoma, Sentinel Lymph Node, Recurrence, Tumor Load

Introduction

In the past decades, the incidence of cutaneous malignant melanoma has risen steadily, accompanied by an increase in mortality in male patients {MacKie et al., 2007, Br J Cancer, 96, 1772-7}. Due to major prevention efforts, the numbers seem to stabilize in younger age groups {MacKie et al., 2007, Br J Cancer, 96, 1772-7}. Early diagnosis has increased the proportion of thin melanomas with a greater likelihood for cure {McMasters and Swetter, 2003, J Surg Oncol, 82, 209-16}.

Gelöscht: and this is

Gelöscht: Moreover, e

Gelöscht: , early-stage

However, the overall melanoma-specific survival remains unaffected despite all endeavors towards improving medical care. Much attention has been focused on the management of the regional lymph nodes (RLN) in melanoma patients.

Gelöscht: We have, h

Gelöscht: not been able to improve

Gelöscht: ,

Gelöscht: treatment both surgically and systemically

Gelöscht: understanding the role and

In this context, the surgical management strategies of the RLN have undergone considerable change in the past; with lymphatic mapping and sentinel lymph node (SLN) identification being the most relevant contribution, {Cabanas, 1977, Cancer, 39, 456-66}, {Morton et al., 1992, Arch Surg, 127, 392-9; Wong et al., 1991, Ann Surg, 214, 637-41}.

Gelöscht: .

Gelöscht: In 1992, based on preliminary work by Cabanas

Based on the concept that the regional lymphatics serve as a barrier, temporarily trapping the orderly tumor spread from the primary site to more distant locations, it was proposed that the histopathological status of the SLN would accurately predict melanoma metastases {Reintgen et al., 1994, Ann Surg, 220, 759-67; Thompson et al., 1995, Melanoma Res, 5, 255-60}.

Gelöscht: , and his own research, Morton et al. introduced the method of sentinel lymph node biopsy (SLNB) into the clinical treatment regimen for patients with primary tumors of intermediate risk

Today, SNB is the most important staging tool, because the status of the SLN presents

Gelöscht: Accuracy and reliability of the method as

Gelöscht: a

Gelöscht: as well as

Gelöscht: as

the most important prognostic factor for recurrence and survival for melanoma patients, and identifies patients, who might benefit from further therapy, such as

Gelöscht: , have since been proven beyond any reasonable doubt

complete lymph node dissection (CLND) and adjuvant interferon therapy {Balch

et al., 2001, J Clin Oncol, 19, 3622-34; Hafner et al., 2004, Br J Dermatol, 150, 677-86;

Morton et al., 1999, Ann Surg, 230, 453-63 discussion 463-5}. {Eggermont AM, 2007,

Gelöscht: The status of the SLN is employed to identify patients, who might benefit from further therapy, such as complete lymph node dissection (CLND) and adjuvant interferon therapy

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18S , 8504 }.

Nevertheless, the impact of SLNB on survival remains unclear. Recently, Morton et al. reported an increased disease free survival with no significant impact on over-all survival {Morton et al., 2006, N Engl J Med, 355, 1307-17}, raising the question whether lymph node dissection is necessary in case of a positive SLN. The identification of predictive factors for non-SLN positivity is a challenge in order to spare SLN-positive patients the morbidity of CLND. Unlike the situation for cutaneous melanoma, widely accepted guidelines exist for breast cancer, which no longer recommend CLND in patients with an SLN-sub-micrometastasis (<0.2mm), since these they are highly unlikely to recur regionally {Fournier et al., 2004, Ann Surg, 239, 859-63 discussion 863-5; Rutgers, 2004, Br J Surg, 91, 1241-2}. We communicate our SLNB experience during a 7-year period, particularly focusing on SLN tumor load, non-SLN-positivity and patterns of tumor recurrence.

Gelöscht: must be performed

Gelöscht: Whereas the benefit of CLND on delaying nodal recurrence has been well substantiated, the procedure's lack of impact on overall melanoma-specific survival has underscored the necessity

Gelöscht: of identifying

Gelöscht: that may predict

Gelöscht: ,

Gelöscht: and thus may help to

Gelöscht: unnecessary

Patients and Methods

Patients

392 patients with cutaneous malignant melanoma underwent SLNB, from the introduction of the method in our institution in October 1999, to December 2005, and were followed up until September 31st, 2006. The median period of observation was 38.8 months.

Technique of SLN Identification, Wide Excision and Sentinel Lymph Node

Biopsy

Most patients had already undergone diagnostic excision of the tumor. All patients underwent WE wide excision of the primary tumor with a safety margin

Gelöscht: elsewhere

of 1 cm for Breslow thickness below 2 mm, and a safety margin of 2 cm for Breslow thickness above 2 mm, in accordance with Swiss guidelines {Dummer et al., 2005, *Dermatology*, 210, 39-44}. Neither the triple technique used to identify and remove the SLNs nor the methodology employed for pathological analysis of the removed lymph nodes differs from that previously described in the literature {Hafner et al., 2004, *Br J Dermatol*, 150, 677-86; Morton et al., 2005, *Ann Surg*, 242, 302-11 discussion 311-3}. Consistent with published guidelines {Cochran et al., 2000, *Cancer*, 89, 236-41}, SLNB was recommended for pathological staging of the RLN in patients with a minimal Breslow of 1.00 mm and no clinical or radiological evidence of melanoma metastasis at the time of diagnosis. SLNB was equally performed in 15 Patients with a smaller tumor thickness, for whom the referring dermatologist urged staging, either because the Breslow value was only slightly below 1.00 mm, or histological review revealed aggravating factors. CLND was recommended for positive SLNs, according to the Augsburg Consensus guidelines {Cochran et al., 2000, *Cancer*, 89, 236-41}. Clinicopathologic characteristics were analyzed, including sex, age, location of the primary tumor, Breslow value and size of metastatic depots.

Disease-free survival (DFS) and primary recurrences were determined separately for SLN positive and SLN negative patients according to the anatomic location of the first recurrence. Local recurrences were defined as satellite recurrence within or up to 3 cm around the wide excision scar; in-transit recurrence was defined as recurrence in the dermal lymphatics between the site of the excised primary tumor and the RNB. Recurrences within the staged regional nodal basin were considered RNB recurrences and distant recurrences as distant skin, nodal or systemic recurrences beyond the staged RNB. 7 patients with positive SLNB refused to undergo CLND.

Gelöscht: analyzed

Kommentar [D2]: Steht unten nochmals

Gelöscht: They were counted as SLN-positive, and were continued to be followed-up at the Department of Dermatology, but their data was not included with the CLND group for further analysis. ¶

Follow-up

Patients were all followed-up in our outpatient clinic, until aftercare for all surgical procedures, including the complications thereof, could safely be terminated. Oncological follow-up was performed in the Department of Dermatology according to Swiss national guidelines using a standardized sequence of imaging techniques {Dummer et al., 2005, Dermatology, 210, 39-44}. Recurrences were registered and patients treated according to the site of recurrence, surgically, systemically or by radiotherapy.

Gelöscht: then continued in the outpatient clinic at

Technique of histopathological SLN work-up

After one day of fixation the SLN was bisected along the long axis of the hilar region. If the SLN was thick the two halves were further cut in 2mm thick sections. Depending on its size the bisected node was embedded in one or more paraffin blocks. Paraplast sections at 5 intervals of 50 µm were prepared from each paraffin block. From each paraplast section four slides were made and stained with Haematoxylin-Eosin and immune stained with antibodies to S-100, HMB-45 and Pan Melanoma Plus s acoording the EORTC recommendations for working-up melanoma SLNs. {Cook et al., 2003, J Pathol, 200, 314-9}. Haematoxylin – Eosin and immune stained sections of all samples were reviewed by one experienced pathologist (DM). There were four different diagnoses based on the recommendations of the International Union against Cancer: (i) no tumour, (ii) isolated tumour cells, (iii) micrometastasis (< 2 mm), and (iv) macrometastasis (> 2 mm) {Hermanek et al., 1999, Cancer, 86, 2668-73}. Since no significant differences between patients with isolated tumor cells and patients with micrometastasis were found, we have summarized both groups under the heading of micrometastasis for this analysis, as described in previous

Gelöscht: The SLN was fixed in formaldehyde 4%.

Gelöscht: s. Between 1999 and 2003

Gelöscht: ,

Gelöscht: changed three times

Gelöscht: In the beginning, one half of the SLN was stored fresh frozen and not investigated. Furthermore only two paraplast sections were made. The current recommendations are to investigate the whole SLN and to prepare of each half six paraplast sections. Therefore negative SLNs of patients with tumor relapse previously worked up according to old EORTC protocols were adapted to the current one before reviewing them

Gelöscht: That means fresh frozen material was re-investigated and additional paraplast sections were done.

Kommentar [D3]: Stimmt das? Single cells – keine CLND, oder?

studies {Carlson et al., 2003, Ann Surg Oncol, 10, 575-81; Pearlman et al., 2006, Am J Surg, 192, 878-81; Roka et al., 2007, Eur J Surg Oncol}.

Statistical Analysis

Statistical analysis was performed using SPSS 13. Statistical comparison between two groups of patients was done using a t-test for continuous variables and a chi-square test for categorical variables. Breslow thickness was log-transformed to reach an approximate normal distribution. Comparison of groups with respect to the endpoint "time to recurrence" has been done using Kaplan-Meier curves and a logrank test. For the relationship between a continuous variable (like log Breslow thickness) and time to recurrence, a Cox regression has been calculated. P-values below 0.05 were considered as significant.

Results

Patient characteristics and regional lymph node basin status

Baseline patient characteristics are summarized in table 1. Male patients were significantly older at the time of diagnosis ($p < 0.0001$, t-test). Breslow values for both sexes do not differ significantly ($p = 0.60$, t-test). Analysis of the location of the primary tumor correlated well with gender-specific differences previously described², with the lower extremity as the most common melanoma site in females, and the trunk in males ($p < 0.0001$, chi-square test). A total of 470 hot nodes were identified, on average 1.2 SLN (range 1 – 3) were removed per patient. A total of 427 RNB were staged in our 392 patients, as in 31 patients, lymphocintigraphy identified SLNs in two RNBs, and 2 patients had hot nodes in 3 RNBs simultaneously. We staged 221 axillary RNBs, 146 in the groin and 52

Gelöscht: Although the m

Gelöscht: seeking medical care for a suspicious skin lesion

Gelöscht: , the

Gelöscht: are strikingly similar and not

Gelöscht: different

Gelöscht: upon lymphoscintigraphy

in the head and neck area. Intercalated nodes (popliteal fossa, cubital fossa, medial bicipital sulcus, lateral chest wall) were identified in 8 patients (2%), in 6 (1.5%) of them in conjunction with either additional inguinal or axillary SLNs. All of these intercalated nodes were tumor-free. The rate of major complications mandating either additional surgery or stationary hospital care was 2.3%. A total of 114 positive SLN (24.5%) in 107 Patients (27.3%) were found. Micrometastatic tumour deposits were found in 66 of 107 (61.7%) patients with positive SLNs, while macrometastases were found in 41 (38.3%) patients. ~~Out~~ of 66 patients with micrometastases, 11 ~~presented~~ isolated tumor cells (10.3%).

Gelöscht: Among the

Gelöscht: were

Gelöscht: with

Table 2 displays a comparison, stratified by age, sex and Breslow thickness, of SLN positive and SLN negative patients. Neither gender was significantly associated with a higher rate of positive SLNs nor, consequently, with a gender-dependant significantly worse prognosis ($p=0.84$, chisquare test). No statistically significant differences were evident for median and mean age in SLN positive and SLN negative groups ($p=0.23$, t-test). Both mean and median Breslow thickness were significantly greater in the SLN positive group ($p<0.0001$, t-test). Stratification of the SLN positive patients according to Breslow values (Table 3) revealed increasing rates of SLN positivity proportional to greater thickness of the primary tumor. Influence of the Location of the primary tumor on SLN positivity was statistically insignificant (Table 4) ($p=0.38$, chisquare test). CLND was recommended to all 107 patients with positive SLNs. 100 (93.5%) underwent the procedure, 7 (6.5%) refused and their data was not included for the outcome analysis of the SLN-positive group.

SLN-Positive Patients - CLND results

We performed a total of 102 CLNDs on 100 patients, as 1 patient had bilateral

axillary CLNDs, and 1 patient had bilateral groin CLNDs simultaneously. In all, 46.1% of all CLNDs were axillary (47/102), 42.2% were in the groin (43/102) and 11.8% were neck dissections (12/102). No additional positive non-SLN was found in 78% (78/100) of the CLNDs, whereas 22% (22/100) had additional positive nodes. SLN tumor load did not effectively predict non-SLN-positivity in CLND: 30.8% (12/39) of the CLND patients with a macrometastasis in their sentinel had further non-SLN-positivity. In comparison, 16.4% (10/61) of those patients with a SLN micrometastasis, had a positive CLND ($p=0.09$, chisquare test).

SLN-positive Patients – Melanoma recurrence

65% (65/100) of patients, who underwent CLND, remained disease-free, 35% (35/100) presented a tumor relapse: Median time to recurrence was 12.5 months (range 3 – 43 months). Primary sites of recurrence were local or in-transit (9/35, 25.7%), nodal (11/35, 31.4%), and distant (15/35, 42.9%). Patients without further positive non-SLNs had significantly less recurrent disease (26.9%, 21/78), compared to those with additional positive non-SLNs in CLND (14/22, 63.3%) ($p=0.001$, logrank test) (cf. Table 5 and Fig. 1a). The effect of tumor load on recurrence was pronounced: In general, recurrence rates in the SLN positive group were 35.0%, and 10.9% in the SLN negative group, the difference being highly significant ($p<0.0001$, logrank test) (cf. Fig. 1d). Among the SLN positive patients, tumor recurrences after a positive SLNB were more than twice as frequent for SLN macrometastases (51.3%, 20/39) than for micrometastases (24.6%, 15/61), the difference being significant in a DFS analysis ($p=0.005$, logrank test) (cf. Fig. 1b). Stratified by size of SLN metastasis and number of additional positive non-SLNs in the CLND, the impact of SLN

Gelöscht: In general, of all patients who underwent CLND,

Gelöscht: whereas the remaining

tumor load becomes even more evident: 51 of the 78 patients with no further positive lymph node in the CLND had micrometastatic tumor depots in their SLNs; 9 of them (17.6%) suffered a relapse. This rate was significantly higher and more than doubled for the 27 patients in whom the SLN, although remaining the only positive lymph node even after CLND, harbored a macrometastasis: 12 patients (44.4%) exhibited tumor recurrences ($p=0.009$, logrank test). Even more impressive was the correlation between additional positive non-SLNs in CLND and tumor recurrence: 66.7% (8/12) of all patients with SLN-macrometastases and 60% (6/10) of patients with SLN-micrometastases who had positive non-SLNs in CLND relapsed during the mean follow-up period of 38.8 months. **The influence of additional positive non-SLNs aggravated tumor recurrence only by increasing total tumor burden and did not exert more prognostic influence than SLN tumor burden alone:** Patients with SLN-macrometastases and positive non-SLNs did not have significantly more tumor recurrences compared to those with SLN-micrometastases and positive non-SLNs ($p=0.60$). SLN tumor burden did, however, influence recurrence significantly when analyzing micro- and macrometastases separately: Whereas for patients with SLN macrometastases, the difference in the development of tumor recurrences did not differ significantly ($p=0.17$) between patients with (recurrence 66.7%, 8/12) or without (recurrence 44.4%, 12/27) additional non-SLNs in CLND, for patients with SLN micrometastases the DFS-analysis was significantly worse when comparing those with additional non-SLNs (60% recurrences, 6/10) to those without (17.6% recurrences, 9/51) ($p=0.003$, log-rank test). This difference did not, however, correspond to significant differences in DFS: Both patients with SLN micrometastasis either with ($p=0.022$, log-rank test) or without additional positive non-SLNs ($P<0.0001$, log-rank test) fared

significantly worse than patients with tumor-free SLNs (cf. Fig. 1c).

For Breslow thickness, another indicator for tumor load, there was also correlation with tumor recurrence: For intermediate thickness melanomas (Breslow 1-4 mm), the rate of recurrence after positive SLNB remained within similar margins. (Table 3). In 27.5% (11/40) of the patients with a primary tumor thickness of 1-2 mm, the tumor relapsed, as well as in 33.3% (11/33) of the patients with a primary Breslow of 2-4mm. The rate of recurrence, however, increased sharply for positive SLNs associated with a primary melanoma thicker than 4 mm: Every second (50%, 12/24) recurred after CLND. The percentage of micro- and macrometastases, however, remained fairly constant and did not increase proportionally with Breslow thickness (Table 3) ($p=0.23$, t-test).

Negative Patients

During the median period of observation of 38.8 months, 89.1% (254) of the 285 negative patients showed DFS. 10.9% (31), however, exhibited recurrences and the SLNB was therefore considered false-negative (FN). Identical false-negative rates were noted for distant (4.2%, 12/31) and nodal primary recurrence. Local or in-transit relapse was seen in 2.5% (7/31). All of the RNBs, in which SLNB was performed, yielded similar rates of false-negative results. 7.7% (17/221) of all staged axillary RNBs produced false-negative results, 6.2% (9/146) were from SLNBs in the groin and 9.6% (5/52) came from Head and Neck RNBs. Median time to recurrence for false-negative SLNB patients was 23 months: 24 month for primary distant relapse, 19 for primary nodal failure and 16 for local and in-transit recurrence.

Discussion

In this single centre retrospective analysis, we reviewed our experience with SLNB in cutaneous melanoma. Our well-characterized patient population was treated and followed using a structured algorithm, and compares well with other series published. Our main objective was to study the correlation between SLN tumor load and further non-SLN-positivity as well as DFS.

Consistent with our own data (78%) 67-90% of SLN-positive patients do not have further non-SLNs that contain tumor deposits in the CLND specimens {Carlson et al., 2003, Ann Surg Oncol, 10, 575-81; Reintgen et al., 1994, Ann Surg, 220, 759-67; van Akkooi et al., 2006, Ann Oncol, 17, 1578-85}. As a consequence, the majority of SLN-positive patients undergoes unnecessary surgery associated with considerable morbidity {Guggenheim et al., 2008, Ann Surg, 247, 687-693}. Therefore, several authors have tried to identify patient, tumor and

SLN characteristics predicting further non-SLN positivity in order to spare CLND {Carlson et al., 2003, Ann Surg Oncol, 10, 575-81; Scolyer et al., 2007, Ann Oncol, 18, 806-8; van Akkooi et al., 2006, Ann Oncol, 17, 1578-85}.

Although CLND has not yet been proven to positively influence overall melanoma-specific survival, Cascinelli et al have recently shown that CLND is necessary to achieve the best assessment of prognosis of stage IB and II melanoma and to identify those patients who, having only positive sentinel nodes and negative nonsentinel nodes, have a good prognosis {Cascinelli et al., 2006, J Clin Oncol, 24, 4464-71}. Whereas previous studies have failed to consistently identify the same clinicopathological features as indicators for additional non-SLN positivity upon CLND or for DFS {Scolyer et al., 2007, Ann Oncol, 18, 806-8}, SLN tumor load, nevertheless, was uniformly confirmed by all of these studies as prognosticator for non-SLN positivity and recurrence. Thus, we focus our analysis on this characteristic.

Gelöscht: Several aspects relating to these objectives are currently debated: ¶
1. Is there a set of characteristics to help reliably identify those SLN-positive patients who do not have further positive non-SLN-positivity and could thus be spared CLND? ¶
2. Can we identify and classify different forms of SLN tumor burden associated with different rates of disease-free and overall survival? ¶

Gelöscht: SLN-dependent prognosticators for non-SLN-positivity in CLND and for DFS ¶

Gelöscht: , which in the case of CLND is fraught with

Gelöscht: SLN-positive patients a procedure without benefit to them

Gelöscht: W

Gelöscht: therefore considered it advisable to

There is considerable debate as to how to stratify SLN tumor burden. Several authors have reported that submicroscopic SLN tumor burden may be without prognostic significance or even judged as SLN-negative: Satzger et al. {Satzger et al., 2007, Am J Surg Pathol, 31, 1175-80} found that isolated immunohistochemically positive tumor cells are without prognostic significance and DFS of these patients did not differ from that of SLN-negative patients, an observation which is supported in a broader sense by Van Akkooi et al. {van Akkooi et al., 2006, Ann Oncol, 17, 1578-85} In their study, no patient with an SLN tumor load of <0.1mm had additional non-SLN-positivity upon CLND, and 5-year overall survival was 100%. On the basis of these data, they suggested that such patients may be considered SLN-negative and should be spared CLND. A similar observation, albeit with a cut-off <0.2mm, was made by Govindarajan et al. {Govindarajan et al., 2007, Ann Surg Oncol, 14, 906-12} Both studies did, however, either not reach statistical significance (Van Akkooi) or the study population was relatively small (Govindarajan). Yet another cut-off based on a novel micromorphometric classification, albeit this time at 1mm above submicroscopic levels, was proposed by Starz et al {Starz et al., 2004, Ann Surg Oncol, 11, 162S-8S}. In his studies, patients with deposits <1mm had survival rates not significantly different from those of patients with tumor-free SLNs. As these results proved to be difficult to reproduce, however, all these observations are contested by other authors {Scheri et al., 2007, Ann Surg Oncol, 14, 2861-6; Scolyer et al., 2007, Ann Oncol, 18, 806-8}. Scheri {Scheri et al., 2007, Ann Surg Oncol, 14, 2861-6} found that 12% of their patients with isolated tumor cells had further positive non-SLNs in their CLND-specimens and that their melanoma-specific survival was significantly worse than in those patients with negative SLNs.

Kommentar [D4]: Diesen Abschnitt ev ganz weglassen. Wir haben unsere Bedingunegn ja definiert..

Gelöscht: ,

Gelöscht: however,

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Formatiert: Englisch (Großbritannien)

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The failure to predict the necessity of CLND based on sub-microscopic SLN tumor load is demonstrated by several studies: Carlson et al. {Carlson et al., 2003, Ann Surg Oncol, 10, 575-81}, reported that 22.6% of patients with isolated tumor cells had further positive non-SLNs upon CLND. Although the numbers are too small to reach significance, our own data from patients with isolated tumor cells indicate that indeed submicroscopic cut-offs and micromorphometric classifications may not contribute much towards clarifying behavioural and prognostic differences according to SLN tumor burden. Of the 11 patients with isolated tumor cells in our series, only 1 (9.1%) had additional positive non-SLNs, but 3 (27.3%) had tumor recurrence during follow-up. The cut-off separating micrometastases from macrometastases at 2mm, as put forth by Hermanek et al {Hermanek et al., 1999, Cancer, 86, 2668-73}, however, may allow more promising conclusions. Several authors have used this cut-off in analysing their study populations. Despite the fact that 6% of the patients with micrometastases (isolated tumor cells not differentiated) in their SLNs had a positive CLND, Pearlman et al. {Pearlman et al., 2006, Am J Surg, 192, 878-81} found that their 5-year survival was at 85% essentially the same as that of patients with a negative SLNB. Carlson et al. {Carlson et al., 2003, Ann Surg Oncol, 10, 575-81} have made a similar observation: Even though SLN tumor burden was not predictive of non-SLN-positivity, the 3-year overall survival for patients with SLN tumor burden $\leq 2\text{mm}$ (including isolated tumor cells) was significantly higher than for those with SLN tumor deposits of $>2\text{mm}$ (90% vs. 57%), irrespective of whether patients had positive CLNDs or not. Roka et al. {Roka et al., 2007, Eur J Surg Oncol} were able to partly confirm this: even though no significant association between SLN tumor load and non-SLN-positivity was found, the rate of DFS for patients with a SLN tumor burden of $>2\text{mm}$ was

Gelöscht: notion that it is impossible

Gelöscht: which patients do not require

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significantly worse. Similar observations come from a study by Ranieri et al.

{Ranieri et al., 2002, Ann Surg Oncol, 9, 975-81}, albeit with a cut-off at 3mm. Our own data confirms these results in part: SLN tumor burden with a cut-off at 2mm was indeed a significant prognosticator for tumor recurrence ($p=0.005$, logrank test), with the rates of relapse during the median observation period more than twice as frequent for SLN macrometastases (51.3%) as for micrometastases (24.6%). Moreover, even though there was no association between SLN tumor burden and additional non-SLN-positivity, there was a clear statistical trend ($p=0.09$) in our study indicating that patients with higher SLN tumor burden might be associated twice as likely with non-SLN-positivity. This finding confirms a similar trend demonstrated by Roka et al. that may reach statistical significance once analyzed in larger study populations {Roka et al., 2008, Eur J Surg Oncol, 34, 82-8}. The rates for positive CLNDs were not significantly different for SLN macrometastases and micrometastases. This is in accordance with other studies in which reproducible prediction of non-SLN positivity on the basis of SLN tumor burden remained elusive {Carlson et al., 2003, Ann Surg Oncol, 10, 575-81; Pearlman et al., 2006, Am J Surg, 192, 878-81; Ranieri et al., 2002, Ann Surg Oncol, 9, 975-81; Roka et al., 2007, Eur J Surg Oncol}. Additional positive non-SLNs upon CLND are widely recognized to adversely influence prognosis

{Carlson et al., 2003, Ann Surg Oncol, 10, 575-81}. In our study, tumor recurrences were significantly more frequent in patients with additional positive non-SLNs in CLND than in those who did not have a positive CLND. Although our study confirms that predicting non-SLN-positivity on the basis of SLN tumor load is unreliable, it demonstrates that SLN tumor burden has an impact on DFS.

Recent experimental studies using melanoma cell lines in mice, have impressively shown that melanoma cells can switch their transcriptional profile

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Gelöscht: Our results further support this observation:

Gelöscht: during the observation period of 38.8 months

Gelöscht: Our results thus underscore how much remains unclear concerning SLN tumor load and possible therapeutic implications. Even

Gelöscht: our data further

Gelöscht: supports the data that

Gelöscht: correlates with differing rates of

from an invasive migrating one to a proliferative profile associated with melanocytic differentiation (Hoek et al. Cancer Res. 2008). We hypothesize that the evaluation of the invasive markers in melanoma mets might improve the predictive accuracy of the SN status.

Gelöscht: Although there is some discrepancy over the exact cut-off point, there is consensus regarding the behavioural and prognostic differences according to SLN metastasis size and burden.

Today, neither clinicopathological nor histomorphometrical characteristics reliably and reproducibly predict non-SLN-positivity in CLND. However, in accordance with several other authors, our study supports the observation that the cut-off at 2mm for SLN tumor load serves to accurately predict differences in DFS. In contrast to other studies, however, patients with SLN tumor burden ≤ 2 mm did have DFS significantly worse than those with tumor-free SLNs. Although far from allowing conclusions, our study illustrates that we do not as of yet sufficiently understand what constitutes relevant nodal disease. Even though CLND has not been proven to improve survival, pending the results of MSLT-II, no clinical recommendations concerning the discontinuation of CLND based on SLN tumor load can be deduced.

Gelöscht: SLN-tumor load stratified along a cut-off at 2mm was reported to correlate with DFS irrespective of positive non-SLNs. Although such a correlation was evident for SLN micrometastases in our series, which were associated with a significantly increased DFS when compared to SLN macrometastases, every single stratification according to SLN tumor burden (with and without additional positive non-SLNs), showed worse rates of DFS for any group of patients with positive SLNs when compared to SLN-negative patients. ¶

Gelöscht: Conclusion:¶
Our data confirms that

Gelöscht: have been identified as of yet which help to